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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,191	06/24/2005	Jeffrey P. Erickson	AIB-09206	5158

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Peter G Carroll
Medlen & Carroll
101 Howard Street
Suite 350
San Francisco, CA 94105

EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,191	ERICKSON, JEFFREY P.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-29,32-35 and 41-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13, 15-29, 32-35, 41-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/5/07 has been entered.

Applicant's arguments filed 2/5/07 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-13, 15-29, 32-35, 41-51 are pending and under consideration. New claim 51 has been added. Claims 14, 30-31, 36-40 are canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 15-29, 32-35, 41-51 as amended or newly added remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an exogenous nucleic acid encoding at least one transgenic polypeptide, said nucleic acid operably linked to a salivary gland-specific cis-acting transcription control region, does not reasonably provide enablement for a transgenic non-human mammal by way of the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a transgenic non-human mammal expressing a polypeptide in saliva at a level of at least 0.5 mg/ml, a method of collecting saliva from the same transgenic non-human mammal, and a method of producing the same transgenic non-human mammal.

The specification has asserted that the invention features transgenic non-human mammals that express transgenic polypeptides in their saliva. The specification discusses that salivary gland and saliva specific regulatory elements are necessary to achieve saliva specific expression of a polypeptide of interest. See pages 26-28 of the specification. However, the guidance provided by the specification does not correlate to use of any particular saliva specific regulatory element for the creation of transgenic non-human mammals embraced by the claims. Moreover, the guidance provided by the specification is general as it does not even disclose which saliva regulatory elements could be used to create any of the transgenic non-human mammals embraced by the claims. Finally, the working examples provided by the specification (see pages 81-101) while exemplifying creation of different transgenic cows that express prothrombin and fibrinogen in their saliva respectively, did not disclose which saliva regulatory elements were used to create the transgenic cows and therefore failed to provide the skilled artisan with adequate guidance to make any of the transgenic non-human mammals embraced by the claims. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

As a first issue, the claims embrace transgenic non-human mammals that express and produce a transgenic polypeptide in saliva. The specification has discussed that saliva specific regulatory elements are necessary to achieve expression of a polypeptide of interest in saliva of a transgenic non-human mammal. See pages 26-29 of the specification. However, the guidance provided by the specification with respect to use of saliva specific regulatory elements

was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (from PSP and B1-Ips genes) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva. This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229), for example on page 217, which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson. Finally, in an attempt to provide guidance as to which saliva regulatory sequence may be used within the scope of the claimed invention, the specification has relied on improper incorporation by reference of subject matter that appears to be essential. See the references to Mikkelsen, Larson and Mirels at pages 27-28 of the specification. Applicant is reminded that subject matter essential to the claimed invention may not be incorporated by reference to a non-patent publication. See 37 C.F.R. 1.57(c) and MPEP 608.01(p). Accordingly, given the lack of guidance provided by the specification, the skilled artisan would not know which regulatory sequence to use to achieve saliva specific expression of a polypeptide in a transgenic non-human mammal. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use any of the transgenic non-human mammals embraced by the claims without a reasonable expectation of success.

As a second issue, while the claims embrace transgenic non-human mammals expressing a transgenic polypeptide in saliva, the working examples provided by specification did not provide adequate guidance that would enable one of skill in the art to create any of the

transgenic non-human mammals embraced by the claims. The working examples (see pages 81-101 of the specification) discussed the creation of separate transgenic cows that expressed prothrombin and fibrinogen respectively in their saliva. However, the working examples failed to disclose which saliva regulatory elements were used in the creation the transgenic cows. As previously stated the specification as a whole has not even identified or provided the regulatory elements necessary to practice the claimed invention. A mere statement that saliva regulatory elements existed and could be used is not sufficient to enable the breadth of the claims as directed to transgenic non-human mammals expressing transgenic polypeptides in saliva. If there is no disclosure of starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art. See Genentech Inc. v. Novo Nordisk A/S 42 USPQ2d 1001, 1997. The art teaches that parotid-specific transgene expression requires an upstream cis-regulatory domain, namely the parotid control region, and this parotid control region functions with a heterologous promoter and is indispensable for achieving transgene expression and deletion of specific regions results in ectopic gene expression and the inducible expression of the transgene expression in transgenic mice decreases over 30-fold (abstract) (**Tu et al**, Gene Expr, 3(3): 289-305, 1993). In this case the starting material that has not been disclosed is the saliva regulatory element necessary to create the transgenic non-human mammals embraced by the claims. Given, the lack of guidance and absence of working examples provided by the specification correlating to creation of transgenic non-human mammals, the lack of guidance provided by the specification with respect to use of saliva regulatory elements, the unpredictability of saliva regulatory elements, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

Applicants argue that salivary protein expression is not promoter specific by providing references where: (a) a single injection of Ad.CMV-cHK at a dose of 4x10(9) pfu resulted in a sustained expression of human tissue kallikrein in rat salivary glands and high level of exogenous protein expression using a PSP promoter in a Lama construct was reported to be a reliable technique, in Wang et al reference, (b) a cassette for high-level expression in the mouse salivary glands is described carrying known regulatory regions in the PSP gene was expressed at high-levels in the parotid glands, in Laursen et al reference and (c) the main regulatory region in the murine PSP gene is a parotid gland enhancer in Laursen et al reference. Applicants argue these teachings should prove highly useful for expression of heterologous proteins in the saliva of transgenic mice, and these teachings clearly indicate that the Applicants specification is enabled for salivary gland protein expression in a transgenic mammal because those having ordinary skill in the art would be aware of the proven state of the art for the Applicants' disclosed promoter expression systems. These arguments are not persuasive. Applicants have not disclosed the use of a CMV driven construct which results in the secretion of a gene in the salivary glands of a mammal at the claimed levels; (b) Applicants have not disclosed the use of a main regulatory region in the murine PSP gene which is a parotid gland enhancer to the production of a polypeptide in a mammal's saliva at the claimed levels. Note Mikkelsen concludes that the endogenous high level of PSP expression in the parotid gland depends on additional regulatory sequences to those included in the Lama construct. Applicants have not disclosed what are the regulatory sequences necessary to achieve saliva specific expression of a polypeptide of interest in a transgenic mammal at the claimed levels. Applicants have not correlated the use of parotid gland expression cassette, carrying all known regulatory regions in the Psp gene to the expression of a heterologous protein in the saliva of a transgenic mammal to overcome the art limitations of using the "known" promoter sequence of the parotid secretory

protein (PSP) gene as discussed by Samuelson. Applicants have not disclosed the main regulatory region or enhancer in the murine PSP gene to achieve the expression of a claimed polypeptide in a transgenic mammal. Note the specification recognizes the importance of regulatory sequences, in addition to the promoter sequences such as enhancers, splice signals, transcription termination signals and polyadenylation sites, among others which are useful regulatory sequences that increase the efficiency of expression of the polypeptide and/or protein of interest in transgenic organisms." (see specification p 34).

Applicants argue the specification relates to regulatory sequences. Applicants argue the Examiner discounts the Applicant's reliance on subject matter known in the art as "improper incorporation by reference" regarding Mikkelsen, Larson and Mirels at pages 27-28 of the specification. Applicants argue that the specification states promoters and regulatory sequences can be obtained by methods well known and readily available in the art and for the Examiner to make a reference to an isolated remark in Samuleson regarding the "limitations" of unknown promoter sequences is not relevant as the Applicant points to specific promoters already known to be usable. These arguments are not persuasive. Applicants have not provided the regulatory sequences by stating the region of 5" flanking DNA required for the salivary gland-specific expression is about 4.6 kb; but longer regions may provide higher levels of expression because the skilled artisan would not know what is the approximation of 4.6 kb and how many sequences are required for longer regions for higher expression levels. Furthermore, Applicants have not taught which saliva regulatory sequences were used to create the transgenic bovine discussed in the working examples. Applicant is reminded that the subject matter essential to the claimed invention may not be incorporated by reference to a non-patent publication. The MPEP states § 1.57 Incorporation by reference.:

> "Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to:
> (1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112;"

Note the specification points to the importance of the regulatory sequences besides the promoter for the claimed invention by emphasizing: "Among the sequences that regulate transcription that are useful in the invention, in addition to the promoter sequences discussed above, are enhancers, splice signals, transcription termination signals and polyadenylation sites, among others. Particularly useful regulatory sequences include those that increase the efficiency of expression of the polypeptide and/or protein of interest in transgenic organisms. Also particularly preferred in this regard are those that increase the specificity of expression in targeted compartments of a transgenic organism. Among highly particularly preferred regulatory regions in this regard are those that increase the efficiency, the specificity or both the efficiency and the specificity of expression in salivary glands, and the production of a desired substance thereby in the saliva of transgenic non-human animals in accordance with the invention." (see specification p 34-35).

Applicants argue that :

> "The Examples Provide Adequate Guidance To Create Transgenic Animals. The Examiner objects to the Examples within the specification because: ... the working examples failed to disclose which saliva regulatory elements were used in the creation of the transgenic cows. The Applicant disagrees and argues that the provided examples are prophetic and draw support from the specification as discussed above and the arguments provided in the previous Office Action response (herein incorporated by reference). The Examiner is reminded that Examples are not required, much less "working examples".

These arguments are not persuasive. Applicants have not provided guidance to the issue of unpredictability of creating all transgenic mammals with said levels of a polypeptide in their saliva without the starting material of specific regulatory regions for creating the construct.

Applicants argue that the provided examples are prophetic and draw support from the specification as discussed above and the herein incorporated by reference. Applicants argue that examples are not required and much less "working examples". These arguments are not persuasive. While it is correct that the working examples are not required, it is asserted that use of saliva regulatory element is unpredictable. It is further asserted that applicants have not provided the specific starting material or the specific regulatory sequences necessary for the creation of the transgenic cow, which produces the polypeptide in the saliva and to correlate the creation of said transgenic cow to a transgenic mammal by way of the claimed methods.

Applicants argue the claims convey germline transmission. As is agreed, upon amendment to the claims, the claims do convey germline transmission.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 51 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 51 recites the limitation "wherein said genome comprises a plurality of cells". It is not clear that the genome which is a component of a cell to comprise a plurality of cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600